Improved Drug Development: An Opportunity for Cooperation and Education

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Testimony for the Hearing Record

"Reauthorization of the Prescription Drug User Fee Act and FDA Reform"

Subcommittee on Health and Environment
Committee on Commerce
U.S. House of Representatives
Congressman Michael Bilirakis, Subcommittee Chairman

Chairman Bilirakis and Members of the Subcommittee. I am Dr. Raymond Woosley, Professor and Chair of the Department of Pharmacology at Georgetown University Medical Center. I am grateful for the opportunity to share my views regarding the opportunities for improved drug development and optimizing utilization of medications by the public. I have three messages that I would like to convey this afternoon. I will list them first and then expand on each:

1. The availability of User's Fees has improved the drug review process but there are costs in addition to the medical reviewer's time spent on the NDA that must be borne by someone.

2. The development time for new drugs and devices can be shorter and still be more informative but it will require a cultural change at the Agency. I suggest that this can be achieved by restructuring the FDA's Advisory Committee function.

3. The FDA should supplement its regulatory and compliance monitoring programs with educational programs that foster optimal utilization of drugs and devices by the medical community and the public.

Users Fees: Over 53 new drugs were approved by the FDA in 1996. 48 of these were under the user fee program. In addition to the cost of reviewing these drugs there is the added burden of safety monitoring. determining how the availability of these drugs influences the labeling of competitors or **older** drugs and revising their labels accordingly. Also. there is the important need for the agency to conduct regulatory research on how it can better perform its mission. There is also the need for the medical reviewers to have meaningful professional development rime. Someone must be willing to pay for these additional costs or the User Fee system will overwhelm the Agency, ultimately endangering the public health and not serving the long term interests of the industry.

Advisory Committees: The Agency has increasing but still limited interaction with sponsors during the development phase of drugs and devices. The final ND.4 is received and the medical officer begins his or her review It then goes to an Advisory Committee which is often a rubber stamp of the medical reviewer's recommendation or too late to be effective. I suggest that the FDA. establish a cadre of independent expert advisors from which the medical reviewers and the sponsors can select a third member(s) to join a team that will shepherd the drug or device through the development process. The outside independent expert can provide mediation in disputes and reassurance when one member of the team mav be in doubt on a decision. The team approach should be both more expeditious and more informative. When the final ND.4 is submitted. there should be no surprises and the review time minimized.

Education as a tool: The agency currently focuses on protecting the public by restricting the availability of potentially harmful drugs and devices. An under used tool to accomplish the same goal is education. I have suggested that the FDA join with academic medical centers to establish regional centers that would carry out educational programs for the public and healthcare providers designed to optimize the use of drugs and devices. These programs would tell the public that when they are given a prescription. they should demand counseling by their physicians and pharmacists. These programs could detect and encourage the reporting of adverse

reactions to drugs and devices. They could warn of the dangers of polypharmacy and the interactions that can occur from mixing drugs and even taking drugs with certain foods. Authorization for these Centers was included in the reform bills considered by the 104th Congress and I encourage you to incorporate it in the current bill.

In summary, in this era of constrained resources I believe that thoughtful reform can enable the FDA to more effectively carry out its mission. However. it will require restructuring of its approach to the review process, its use of outside experts and better utilization of tools such as educational programs.

Centers for Education and Research in Therapeutics

The United States of America is a medication-oriented society. Each year over 2 billion prescriptions are written, amounting to over eight prescriptions per person. Over two thirds of patient visits to physicians result in at least one new prescription; and often more than one. Over $60 billion is spent each year on prescription drugs and much more on non-prescription drugs. All will agree that medications have contributed positively to our Nation's overall public health and the pharmaceutical industry is to be commended for developing the drugs that have led to major advances in medical care. However, are we utilizing these therapies optimally? Are physicians, nurses, pharmacists and the public being taught how best to use these drugs? Prescribing errors are the second largest cause for a malpractice claim in the US today. Of these errors, 42.4 percent result in death or permanent disability. Fifteen percent of hospitalized patients suffer a significant adverse reaction to a medication and five percent of medical admissions to hospitals are due to adverse drug reactions. Recent estimates indicate that at least 25 percent of prescriptions for the elderly are inappropriate and dangerous. Polypharmacy results in serious and potentially lethal drug interactions with more and mare new drugs, such as the newer antihistamines. There is an unmet need to provide physicians more complete information about the drugs they prescribe. The pharmaceutical industry mainly promotes a drug's advantages in approved indications. At the same time the manufacturer is prohibited from promoting unapproved uses of drugs, even if efficacy is generally accepted.

Another important deficiency in our therapeutic knowledge base stems from limitations in the basic and clinical research on the actions of drugs. After demonstrating efficacy and relative safety the pharmaceutical industry, of necessity, invests its resources into finding the positive attributes of its drugs. Yet, there is additional important research that is not being conducted. e.g. studies of the biochemical or pharmacogenetic mechanisms for drug Interactions or adverse drug reactions, actions of drugs in special populations (pediatrics, the very elderly, women, minorities) and efficacy for less than profitable indications. The Nation's academic medical centers have the pharmacologic expertise to conduct this research and they have the trained educators qualified to teach practicing physicians, nurses. pharmacists and the public about the drugs that they prescribe, administer or purchase.

A program of federally-authorized regional academically-based Centers for Education and Research in Therapeutics (CERT) has been proposed as a solution to this problem'. The Centers should be selected by an NIH peer-review mechanism and affiliated with the FDA for coordination of their basic and clinical research. The Centers would include pharmacologists. clinical pharmacologists and clinical pharmacists, all conducting needed research and working with the US Pharmacopeial Convention to educate physicians, nurses. pharmacists and the public about the optimal use of medications. The CERT program should allow participation of scientists in the pharmaceutical industry. However, tc assure their objectivity each CERT should be given independent funding. Legislators are encouraged to enact legislation authorizing the CERT program and to appropriate funds so that these Centers can carry out the mission of conducting independent education and research in therapeutics for our Nation.

1. Woosley. R.L.. CERT. Clin. Pharm. Ther. 55:249-255, 1994.

Clinical Drug Development May Soon be Accomplished in Less than 3 Years: Will FDA and the Pharmaceutical Industry be Ready?

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accompanied by

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ABSTRACT

We envision that clinical drug development could be accomplished efficiently and safely in less than 3 years in the future. However, "Reforms" are necessary in all sectors involved (pharmaceutical industry, FDA, and academia) in order to achieve this breakthrough.

The **Collaboration on Drug Development Improvement (CDDI)** comprises here-to-fore voluntary initiative among the three sectors that aims to identify approaches for substantially improving the development practices for new therapeutic agents, **Consideration should be given to funding the CDDI initiative through the reauthorization of PDUFA or via Congressional appropriation.**

The Prescription Drug Users Fee Act (PDUFA) has achieved its goals of predictable FDA review times. **However, the unintended consequences of curtailed regulatory research in CDER and constrained professional development of its review scientists impeding adeauate ureparation for its role in future drug development and regulation.**

A solution to the problem of dissemination of information on off-label uses of approved drugs would be the creation of academic **Centers for Research and Education in Therapeutics** (CERT) to provide unbiased information and needed research on off-label uses. **CERT should be considered for funding via PDUFA or FDA annronriation.**

Quantity and quality of evidence required to establish proof of effectiveness is inconsistently applied by FDA. **FDA's clarifications of this explain the**

rationale for oast and nresent policies but fall short of embracing the full breadth of modern scientific concepts and techniques of effectiveness demonstration.

A new process for anneal and resolution of scientific disagreements between FDA and industrial or academic scientists is needed with mechanisms to guarantee no FDA retaliation against those who engage the process.

Reauthorization of PDUFA is an important opportunity to considerfunding mechanisms for innovative programs (CDDI, CERT), critical FDA scientific staff activities (regulatory research at CDER and professional development), and key FDA reforms (evidentiary standards of effectiveness and dispute resolution).

INTRODUCTION

Good afternoon Chairman Bilirakis and Members of the Subcommittee. I am honored to be invited to share my views regarding drug development and regulation, particularly on reauthorization of the Prescription Drug User Fee Act and FDA reform

My name is Carl Peck. I am a physician trained in mathematics and chemistry, and Board Certified in Internal Medicine and Clinical Pharmacology. I direct the Center for Drug Development Science (CDDS) at Georgetown University Medical Center, where I am Professor of Pharmacology and Medicine. CDDS is an independent academic institution that maintains conflict-of-interest free collaborations with industry, government and other academic scientists. Prior to establishing the Georgetown Center in 1994, I served for 26 years in the U.S. Army Medical Research and Development Command and the U.S. Public Health Service. From 1987 to 1993 I was Director of FDA's Center for Drug Evaluation and Research, during which time I participated in the groundwork for implementation of the first Prescription Drug User Fee Act.

I founded the CDDS to advance the practices of drug development to vastly improve levels of informativeness and efficiency. We are achieving this through research. education' and technical assistance programs. Coordinated by a small staff, our international network of academic, industry and regulatory scientists are identifying key opportunities for improvement of drug development programs. In order to maintain a practical focus. Center faculty, staff, and associates work directly with pharmaceutical

[1] CDDS has recently sponsored a series of international workshops on methodological advances in clinical drug development. including compliance assessments in clinical trials, computer simulation of clinical trials, and accelerated clinical development of active metabolites and stereoisomers. The Center's first full educational course. "Clinical Development of New Drugs and Therapeutic Agents: Art, Science, and New Frontiers" will take place at Stanford University, July 8-11, 1997.

developers in planning, analyzing and guiding actual drug development programs.

A CDDS Vision of Drug Development in the Near Future

We envision a very different paradigm for drug development than exists today. This paradigm will be dependent on conditions and incentives that favor innovation in scientific methods and management practices in evaluating new therapeutic agents. Our vision contrasts sharply with contemporary practices that involve tens to hundreds of clinical trials that may be flawed or have failed in design or performance, and excessive numbers of trial subjects, observations, and costs that require many years to accomplish. We propose a highly compressed, critically informative, efficient and economical development approach that entails two developmental scientific investigations and one clinical trial confirming effectiveness. These are:

1. **Clinical Pharmacology in Normal Human Subjects or Mildly Ill Patients** -- a comprehensive, exploratory clinical investigation in normal subjects or patients to determine a drug's actions in humans.
2. **Clinical Pharmacology in Ill Patients-a** scientifically rigorous, proof-of-therapeutic-concept investigation in patients with a targeted disease that documents discovery of optimally safe and effective dosage.
3. **Confirmatory Effectiveness Trial** -- an unequivocal demonstration of effectiveness and safety in a multi-center (and possibly multi-national) clinical trial. with an adequate number of subjects receiving the new therapy under typical conditions of use.

A small number of developmental investigations, such as bioequivalence or drug interaction trials, may also be undertaken in conjunction with the three principle investigations. **Using this approach, clinical drug development time from IND approval to NDA filing dates should be less than 3 years for most new drugs.** Extensions beyond 3 years of clinical development might occur for confirmatory trials of new treatments for slowly progressing chronic diseases.

Much of the knowledge and technology for achieving this new paradigm is already available or is rapidly emerging. Modem clinical pharmacology enables discovery of what a patient's body does to an administered drug (pharmacokinetics) and what a drug does to a patient's body (pharmacodynamics). Clinical trial designs and data analysis techniques for confirmatory effectiveness testing are well known. CDDS is researching emerging technologies for facilitating improved drug development efficiency such as computer simulation of clinical trials[2].

To achieve this goal of an improved drug development process, all groups involved must work collaboratively. We believe that the CDDI initiative (described below) is an important pathway to this breakthrough in drug development practices.

Collaboration on Drug Development Improvement (CDDI)

On May 2, **1996,** I presented my views to your subcommittee on whether it is

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Although **computer simulation in product development is extensively used in many non-pharmaceutical industries** (e.g. **aerospace. automotive and computer), this technology has not been developed far planning** and **optimizing clinical** trials. **Since its inception, CDDS has championed the development, evaluation, and application of simulation of clinical trials as a new tool to increase the quality and success potential of clinical** trials. **The Center will sponsor a conference on simulation of clinical trials, "Modeling and Simulation and Analysis Workshop: Tools for Efficient Clinical Trials", Washington DC, November** 10-**II. 1997.**

possible to facilitate the development and approval of new drugs and biological products without compromising safety and effectiveness[3]. I focused on the need for bold improvement in drug development practices, particularly in reducing the number of flawed, failed, or unnecessary human clinical trials. Citing the FDA's and the pharmaceutical industry's shared responsibility for improving drug development, I described a pathway for improvement using advances in drug development science, especially clinical pharmacology and statistical data analysis techniques for proving effectiveness. I predicted that streamlining and modernization of effectiveness testing methods could result in reductions in drug development times and more successful employment of human research subjects.

Following the Subcommittee Hearing on June 17-18, 1996, CDDS co-sponsored with FDA (CDER) and FDLI a public conference, "Drug Development: Who Knows Where the Time Goes?". Participants were informed of the strengths and weaknesses of contemporary drug development practices by academic, industry and regulatory scientists. Significantly, attendees to the conference recommended that a formal collaboration among the three sectors be initiated with the goal of identifying approaches for substantially improving the development practices for new therapeutic agents.

Promptly following the conference, the Collaboration on Drug Development Improvement (CDDI) was founded (Appendix 1). Driven by key scientists at CDER (especially Drs. Janet Woodcock and Roger Williams) and CDDS, the representation on the CDDI Steering Committee was broadened to include representatives from CBER,

[3] "Streamlining and Modernizing Drug Development", Testimony by C. Peck for the Hearing Record, Subcommittee on Health and Environment. U.S. House of Representatives, May 2, 1996

PhRMA, and BIO. The Steering Committee met on September 25 and December 5, 1996, to establish the purpose, scope, goals, and future actions. An issues identification meeting is planned for the near future to begin the real work of the CDDI. **However, the lack of funding for this voluntary initiative is jeopardizing its ability to continue its programs. We recommend that your subcommittee consider PDUFA or Congressional appropriation as funding mechanisms for the CDDI initiative.**

PDUFA: Accomplishments and Unintended Consequences

The Prescription Drug User Fee Act (PDUFA) is a great success, Since its implementation in 1993, to the credit of the leadership and scientific review staff of FDA and the new drug sponsors submitting high quality New Drug and Product License Applications (NDAs and PLAs), review times of priority and standard NDAs and PLAs have been reduced to 6 to 12 months. Moreover, the substantial review backlog has been eliminated. FDA is now properly attending to the processes and procedures necessary to meet review time standards. Congress, PhRMA, BIO, and FDA all deserve acknowledgment for their contributions to this landmark achievement.

However, there have been two unintended consequences of the restricted uses of PDUFA derived funds and application review time commitments (coupled with limited non-PDUFA operational resources): critical regulatory research" in CDER, such as

[4] CDDS recognizes that focused. applied regulatory research at FDA is necessary for advancing the scientific basis for regulatory standards (e.g. manufacturing quality assessments, bioequivalence study procedures based on pharmacodynamic endpoints, pharmacometric and simulation based investigations of regulatory value, validation procedures for surrogate endpoints, etc.) and adverse reaction database derivation and analyses. A zero-based assessment of all FDA research should be undertaken and basic research that is not immediately relevant to regulatory standard setting or enforcement should be redirected or transferred to an appropriate government institution (e.g. NIH).

surveillance of adverse reactions, has been curtailed, and professional development of its scientific staff has been constrained. Because **FDA's capacity to implement significant reforms to prepare for its advisory and regulatory roles in future drug development is critically compromised by these deficiencies, reauthorization of PDUFA should not be undertaken without their resolution.**

Some FDA Reform Issues:

Dissemination of off-label uses of approved drugs and Centers for Research and Education in Research (CERT). Physicians must have access to current, **scientifically** reliable and balanced information about drugs in order to make informed decisions for their patient's treatment. Pharmaceutical and device companies should be permitted to disseminate copies of peer-reviewed scientific articles that report scientifically sound clinical trials that have evaluated off-label indications for their products. The companies should be required to disclose their financial interests and that the indication is not FDA-approved. i.e. "off-label," However, dissemination of this information should be monitored by an independent body prepared to respond to prescribing physicians, health care professionals and the public with balanced, unbiased information about the off-label uses of drugs.

The Nation's academic medical centers have the medical, pharmacological, and educational expertise to teach practicing physicians, nurses, pharmacists and the public about drugs that are prescribed, administered, dispensed or purchased. A consortium of federally-authorized regional academically-based centers (CERT) has been proposed as a

means to address this problem (Appendix 2). The consortium would be selected through a peer-review mechanism and would be affiliated with FDA so that activities will be coordinated at a national level. Each Center would include pharmacologists, clinical pharmacologists and clinical pharmacists, all conducting needed research and educational programs about the optimal use of medications. CERTs should include participation of scientists in the pharmaceutical industry; however, to ensure their objectivity, each CERT should be given independent funding. This independence that allows them to be credible advocates for optimal prescribing. These Centers also should conduct research that industry is unlikely to perform, such as the study of unprofitable off-label indications, and the use of medications in children, the elderly and other understudied populations. **We recommend that your subcommittee consider** PDUFA or **directed appropriations to FDA as funding mechanisms for the CERT initiative.**

Standards of Evidence of Effectiveness. As a result of the 1996 Senate and House Hearings on FDA reform the FDA Draft Guidance, "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" was published on March 13, 1997. Prompted by CDDS testimony on the redundant requirement in modem development programs for more than one confirmatory clinical trial to prove effectiveness, FDA scientists have prepared a comprehensive statement of the Agency's current policies and views on the legal and scientific aspects of quantity and quality of evidence necessary to support effectiveness of new therapeutic agents. FDA deserves credit for its review and explication of its policies on this issue. **Nevertheless, FDA's**

draft guidance falls short of embracing the full breadth of cutting edge, scientific concepts and techniques of effectiveness demonstration. CDDS is preparing a detailed critique of the draft guidance to be submitted to the Agency as a public comment.

Scientific Dispute Resolution and Appeals. Aside from many useful guidances and policy statements the Agency promulgates, there are and always will be disagreements over what constitutes sufficient quality and quantity of data to support FDA's conclusions about the safety and effectiveness of new therapies, as well as the investigations necessary to generate such data. Many new drugs for medical conditions with no available effective treatments are novel. The standards of evidence for these new therapeutic agents are sometimes arbitrarily established by the FDA reviewing division with insufficient input from external scientific experts. Currently, the only mechanism to resolve scientific disagreements about test methods, and what outcome measures and/or quantity of data are sufficient. is to bring the issues to the Division, Office or Center Directors. While FDA's standing advisory boards can be called upon to resolve such disputes. in practice many real or perceived disincentives and barriers mitigate this option. Drug developers fear retaliation and retribution when the FDA is not supported in the appeals resolution and often decline to enter into the existing appeals procedure.

To facilitate more efficient resolution of standards of evidence disputes, language could be included in PDUFAII that establishes a mechanism that involves external expert scientists in the IND phase of drug development to recommend to the FDA and the develoner what aualitv or quantity of evidence should be generated

to establish specific safety and/or effectiveness claims. At the request of the sponsoring company, the company and the agency jointly could create the expert panel to resolve disagreements. **An administrative tracking mechanism should be established to ensure that companies that engage the dispute resolution procedure are not penalized in future interactions with** FDA.

"Reform" of All Sectors Involved in Drug Development is Necessary

During the May 2, 1996, Subcommittee Hearing, I presented preliminary results of a pilot study of the contents and qualities of NDAs approved by FDA during 1994-1995, from which we concluded that vast improvements on contemporary drug development are warranted. At that time, our examination of data from 9 of the 52 approved NDAs indicated that contemporary drug development programs appeared to comprise large numbers of clinical trials (44-600+), many of which were not adjudged by FD.4 to be necessary or of high quality (9%-65%). We have recently expanded this pilot study to 24 NDAs. While our conclusions regarding improvability of drug development remain unchanged, the wide variability in content and quality of these successful programs may provide insights into pathways for improvement. For example, several NDAs were approved with fewer than 10 clinical trials, and FDA adjudged some of these programs to have few, if any, flawed or failed trials.

Thus, we remain convinced that all sectors involved in drug develoomeent can and should be "reformed." To be sure, many pharmaceutical firms have been reengineering their approaches to drug development toward fewer, more successful

clinical trials. Nevertheless, inefficient and suboptimal practices persist in contemporary drug development, due in part to lack of carefully evaluated new approaches as well as to lack of receptivity of some (not all) FDA staff to newer and novel scientific methods. Although academia is increasingly involved in performance of clinical trials of new therapeutic agents, it has received few incentives to respond to the need to invent and investigate novel methodological approaches to scientific drug development.

Reauthorization of PDUFA is an important opportunity to consider funding mechanisms for innovative programs (CDDI, CERT), critical FDA scientific staff activities (regulatory research at CDER and professional development), and key FDA reforms (evidentiary standards of effectiveness and dispute resolution).

APPENDIX 1

PROPOSAL

COLLABORATION ON DRUG DEVELOPMENT IMPROVEMENT (CDDI)

CBER, FDA
CDER, FDA
CDDS, Georgetown University
BIO
PHRMA

January 21, 1997

Draft Version 1.0

I. INTRODUCTION

This proposal describes an effort, the Collaboration on Drug Development Improvement (CDDI), that is designed to advance the development process for pharmaceuticals and biopharmaceuticals (medical products). The information developed by the Collaboration will be used to support guidance documents for pharmaceutical scientists on efficient, scientifically sound approaches for development of an investigational medical product. Participating organizations in CDDI are: 1) the Center for Biologics Evaluation and Research (CBER)/FDA; 2) the Center for Drug Evaluation and Research (CDER)/FDA; 3) Georgetown University Medical Center/Center for Drug Development Science (GUMC/CDDS); 4) the Pharmaceutical Research and Manufacturers of America (PhRMA); and 5) the Biotechnology Industry Association (BIO).

II. RATIONALE

Modern drug development requires information to support the translation of candidate therapeutic agents into therapeutically useful products. This information is used to document the utility of new medical products and to satisfy societal interests in allowing safe, effective, and well-labeled medical products into the marketplace. Development of the necessary information to document safety, efficacy, and utility, and to support product labeling involves a highly complex set of scientific and administrative activities. These activities are affected by the needs and interests of the patient and the health care professional, by scientific opportunities, by public health objectives, by commercial factors, and by resource constraints. The scientific framework in which development of a medical product proceeds is dynamic in that new approaches may be developed and older ones discarded. The science-based regulatory framework for development of medical products is also dynamic in that public health objectives may change in response to patient needs and societal interests. Given the dynamic character of these factors and also that the process involves many constituencies-pharmaceutical sponsors, the scientific and health care communities, the government, and society at large--a potential synergism exists in which involved constituencies could work collaboratively to improve methods and procedures for development of new medical products.

III. BACKGROUND INFORMATION

Current approaches to the development of useful information about investigational medical products may require excessive time and effort, leading to delay in the availability of needed treatments. In addition, improvements in the way this information is developed could lead to optimal product labeling and use. To address these issues, the Georgetown University Center for Drug Development Science (CDDS), CDER, and the Food and Drug Law Institute sponsored a meeting in June 1996 entitled *Drug Development:* Who *Knows Where the Time Goes.* The principal goal of the conference was to explore the process that generates information about new medical products and to consider what barriers and constraints exist *in* the process. Following a series of presentations from industry, agency and academia representatives, a panel of experts summarized the presentations and proposed a further collaborative effort to improve methods and procedures for development of new medical products. Following the June 1996 meeting, further discussions occurred to consider the proposals arising from the Georgetown Conference. On September 25, 1996, representatives of Georgetown University Medical Center/CDDS, CDER, CBER, PHRMA, and BIO met and

agreed to consider formation of a collaborative effort, the Collaboration on Drug Development Improvement (CDDI).

IV. PRIOR FDA EXPERIENCE WITH COLLABORATIVE APPROACHES

FDA has worked collaboratively with extramural constituencies on several occasions. Examples include: 1) the National Center for Food Safety and Technology (Attachment **A);** 2) the Joint Institute for Food Safety and Applied Nutrition (Attachment B); and, 3) the collaborative product quality research at the University of Maryland at Baltimore (UMAB). which included scientists from FDA, the pharmaceutical industry, and academia (Attachments C and D).

V. PROPOSAL

The mission, scope, goals and objectives, structure, and process of CDDI are discussed in the following paragraphs.

A. Purpose

The purpose of CDDI is to improve substantially the development of pharmaceuticals, including biopharmaceuticals.

B. Scope

The scope of CDDI comprises the preclinical and clinical testing phases in the development of pharmaceuticals, including the post-approval phase. Drug development science and science management methodologies will both be considered.

C. Goals

CDDI will study and advance current and new approaches to substantially improve the efficiency of the drug development and assessment processes by: 1) reducing unnecessary studies and activities; 2) increasing useful information; and 3) improving resource utilization and shortening development times.

D. Structure and Function

Steering Committee

CDDI will be directed by a Steering Committee. Members of the Steering Committee will consist of the Directors of CBER and CDER, one or more representatives from academia, and representatives from PHRMA and BIO. Steering Committee membership should be composed of individuals with science/technical backgrounds and who also have experience in management.

Technical Committees

Six technical committees will be formed to cover the following areas: 1) Nonclinical Studies; 2) Mechanistic Studies; 3) Empirical Studies; 4) Post Marketing Studies; 5) Science Management; and 6) Novel Approaches. The six technical committees will propose, for Steering Committee approval, programs and projects to develop information to support recommendations to pharmaceutical scientists which may be published as guidance (regulatory and non-regulatory) documents. 'Information' in this context is used broadly to include retrospective and prospective investigations, cumulative understanding of current approaches, literature searches, and associated efforts. Technical Committee members shall possess strong science/technical skills and have experience in the management of science projects.

Working Groups

These groups will supervise the execution of specific projects within a program, work with research site(s) to summarize and report results, and create draft recommendations for further consideration by the supervisory Technical Committee and Steering Committing. Individuals selected for specific working groups should also have strong science/technical skills in specified program/project areas.

E. Process

The Steering Committee will provide general direction to CDDI and oversight to the Technical Committees, including approval of Technical Committee proposals. The Steering Committee will also review outcomes from programs and projects submitted by a Technical Committee, assess the overall impact of CDDI activities, and determine the need for continuing activities and/or modification in the way the initiative operates.

Technical Committees will define programs and projects within programs, create working groups to focus on these programs and projects, and establish timeframes for completion of work. The Technical Committees will review reports and other information generated from working groups, consider how this information can be used in the drug development and regulatory processes, and make recommendations to the Steering Committee.

Working Groups for specific projects within programs will formulate the intended improvement in drug development as the primary goal of a project. Projects may be executed using academic facilities and staff, industry facilities and staff, and/or agency facilities and staff. Selection of a specific site or sites for conduct of a research project will be the responsibility of the Working Group, with endorsement by the supervising Technical Advisory Committee. Consideration of certain projects may occur competitively via a request for proposal process. A peer review process, executed by the Working Group. with final endorsement by the Technical Advisory Committee, will be established to evaluate competing proposals. After completion of a project, the Working Group will work with the project research site to disseminate the results. Dissemination may occur via publications, workshops, and presentations at meetings of professional societies. Results will also be presented to regulatory agency staff associated with or otherwise interested in the research.

A Working Group will collaborate with the project research site to draft guidance documents for review and endorsement by the Technical Advisory Committee, These will be forwarded to the Steering Committee for concurrence and then to appropriate CBER and CDER policy units for further consideration and, if appropriate, translation into regulatory guidances. Policy units within CDER include the Medical Policy Coordinating Committee and the Pharmacology/Toxicology Coordinating Committee.

Regulatory documents developed by these coordinating committees are submitted to the Director, Regulatory Policy Staff, CDER, and to CDER management for concurrence, finalization, and dissemination. [Need equivalence statements for CBER.] Further review by agency management and counsel is performed as necessary. Regulatory guidance documents developed as a result of an initiative effort will be published in the Federal Register. Efforts by a technical committee and a working group may also lead to non-regulatory policy and publications that may be useful to pharmaceutical sponsors.

Training Programs When appropriate, a Working Group and the project research site may be requested to develop training modules to aid in the implementation of new regulatory policy recommendations. Training may occur for agency and non-agency staff and other interested individuals. The Working Group, the Technical Committee, and the Steering Committee will work to monitor the impact of regulatory and other policy arising as a result of research programs, address certain questions that may arise as a policy based on a research project/program is implemented, and assist in updating policy as appropriate.

VII. ADMINISTRATIVE ISSUES

A. Governance

One or more memoranda of agreement or cooperative agreements may be developed by CDDI to facilitate the generation of information by the collaboration.

B. Resources

Resources to support CDDI activities could occur in the form of contributions of 1) personnel time, 2) space, and 3) equipment. Financial contributions may derive from public funds (appropriated dollars), public funds associated with PDUFA, and contributions from specific members and groups. For the latter, two general approaches may be considered. One approach is based on funding programs/projects by collaboration members who have an identified interest in a specific research program/project and regulatory outcome. A second approach involves regular contributions by interested participants which are not linked to a specific research program. The second approach allows general functioning of the collaboration over a specified period of time.

C. Access and Transparency

CDDI deliberations, efforts, and outcomes are expected to be publicly available. The collaboration will develop mechanisms to achieve this objective.

D. Confidential Commercial and Trade Secret Information

CDDI is not intended to disseminate or impact in any way on confidential commercial or trade secret information developed by a pharmaceutical sponsor.

E. Legal Considerations

Cooperative agreements, conflict of interest, intellectual property rights, liability, and other issues, may require consideration by CDDI.

F. National and International Connections

CDDI may work to develop connections with national and international professional societies, academic institutions, and regulatory agencies.

G. Communications and Record-Keeping

CDDI will develop mechanisms to facilitate communications between participants and to maintain records of its activities.

Appendix 2

Centers for Education and Research in Therapeutics - CERT

The United States of America is a medication-oriented society. Each year over 2 billion prescriptions are written, amounting to over eight prescriptions per person, Over two thirds of patient visits to physicians result in at least one new prescription; and often more than one. Over $60 billion is spent each year on prescription drugs and much more on non-prescription drugs. All will agree that medications have contributed positively to our Nation's overall public health and the pharmaceutical industry is to be commended for developing the drugs that have led to major advances in medical care. However, are we utilizing these therapies optimally? Are physicians, nurses, pharmacists and the public being taught how best to use these drugs? Prescribing errors are the second largest cause for a malpractice claim in the US today. Of these errors, 42.4 percent result in death or permanent disability. Fifteen percent of hospitalized patients suffer a significant adverse reaction to a medication and five percent of medical admissions to hospitals are due to adverse drug reactions. Recent estimates indicate that at least 25 percent of prescriptions for the elderly are inappropriate and dangerous., Polypharmacy results in serious and potentially lethal drug interactions with more and more new drugs, such as the newer antihistamines. There is an unmet need to provide physicians more complete information about the drugs they prescribe. The pharmaceutical industry mainly promotes a drug's advantages in approved indications. At the same time the manufacturer is prohibited from promoting unapproved uses of drugs, even if efficacy is generally accepted.

Another important deficiency in our therapeutic knowledge base stems from limitations in the basic and clinical research on the actions of drugs. After demonstrating efficacy and relative safety the pharmaceutical industry, of necessity, invests its resources into finding the positive attributes of its drugs. Yet, there is additional important research that is not being conducted, e.g. studies of the biochemical or pharmacogenetic mechanisms for drug interactions or adverse drug reactions, actions of drugs in special populations (pediatrics, the very elderly, women, minorities) and efficacy for less than profitable indications. The Nation's academic medical centers have the pharmacologic expertise to conduct this research and they have the trained educators qualified to teach practicing physicians, nurses, pharmacists and the public about the drugs that they prescribe, administer or purchase.

A program of federally-authorized regional academically-based Centers for Education and Research in Therapeutics (CERT) has been proposed as a solution to this problem'. The Centers should be selected by an NIH peer-review mechanism and affiliated with the FDA for coordination of their basic and clinical research. The Centers would include pharmacologists, clinical pharmacologists and clinical pharmacists, all conducting needed research and working with the US Pharmacopeial Convention to educate physicians, nurses, pharmacists and the public about the optimal use of medications. The CERT program should allow participation of scientists in the pharmaceutical industry. However, to assure their objectivity each CERT should be given independent funding. Legislators are encouraged to enact legislation authorizing the CERT program and to appropriate funds so that these Centers can carry out the mission of conducting independent education and research in therapeutics for our Nation.

1. Woosley, R.L., CERT, Clin. Pharm. Ther. 55:249-255, 1994.

I disclose that neither the Georgetown University Center for Drug Development Science nor I have received federal funds or federal grants during the past fiscal year or during the two previous fiscal years.

Carl C. Peck, M.D.

April 23, 1997

Date

Dr. Raymond L. Woosley

Agency	Contract #	Title, Funding Dates and Funding Amount
NIH	HL54590	Arrhythmogenic Actions of Antihistamines. 8/1/95-7/31/00: $947,949 Direct Costs
FDA	223-93-3011	Evaluate the Status of Selected Drugs for Conducting In-Vivo Studies and Provide the FDA Access to a Clinical Research Facility. 9/3/93-6/30/97: $2,396,881 Direct and Indirect Costs

I disclose that this is current federal funding.

Raymond L. Woosley, M.D., Ph.D.

4/23/97
Date

CURRICULUM VITAE
Raymond L. Woosley, M.D., Ph.D.

Personal
Born October 2, 1942, Edmonson County, Kentucky
Married, Julianne B. Woosley
Member, Foundry Methodist Church, Washington, DC

Education

1964 - B.S.	Western Kentucky University, Bowling Green, KY (Chemistry and Biology)
1967 - Ph.D.	University of Louisville, Louisville, KY (Pharmacology)
1973 - M.D.	University of Miami, Miami, FL

Internship and Residency

1973 - 1976	Vanderbilt University Hospital, Nashville, TN (Grant Liddle, M.D., Medicine)

Post-doctoral Fellowships

1961 - 1968	University of Louisville, Louisville, KY (K.C. Huang, M.D., Ph.D., Pharmacology)
1976 - 1977	Vanderbilt University, Nashville, TN Departments of Pharmacology and Medicine, Division of Clinical Pharmacology (John Oates, M.D., Clinical Pharmacology)

Professional Experience

Meyer Laboratories, Fort Lauderdale, FL (currently Glaxo-Wellcome)

1968 - 1971	Senior Pharmacologist/Director of Research

Vanderbilt University, Nashville, TN

1976 - 1977	Instructor, Departments of Medicine and Pharmacology
1971 - 1979	Assistant Professor of Medicine and Pharmacology
1979 - 1984	Associate Professor of Medicine and Pharmacology
1981 - 1988	Associate Director, Clinical Research Center
1984 - 1988	Professor of Medicine and Pharmacology

Georgetown University School of Medicine, Washington, DC

1988 - 1994	Professor of Pharmacology and Medicine Chairman, Department of Pharmacology Division Chief, Clinical Pharmacology, Department of Medicine

Updated April *14,1997*

Professional Experience (cont'd.)

1994 - present Professor of Pharmacology and Medicine
Chairman, Department of Pharmacology
Interim Director, Institute for Cardiovascular Sciences at Georgetown

Stanford University **School of Medicine, Stanford, CA**
5/95 - 12/95 **Visiting Professor**
Dept of Molecular Pharmacology

Medical Licensure State of Tennessee, License No. 8681, 7/16/76 - present
District of Columbia, License No. 17237, 4/28/88 - present

Certifications National Board of Medical Examiners, 1973
American Board of Internal Medicine - Certificate No. 55994, 6/16/76
American Board of Clinical Pharmacology - 1991

Awards and Distinctions

1960 -	Valedictorian, Bowling Green High School, Bowling Green, KY
1960 - 1964	Ogden Scholarship, Western Kentucky University
1964 - 1967	NIH Predoctoral Fellowship, University of Louisville, Department of Pharmacology
1967 - 1968	NIH Postdoctoral Fellowship, University of Louisville, Department of Pharmacology, Competitive Award from NIGMS
1974	Fellow, American College of Clinical Pharmacology
1976	NIH Postdoctoral Fellowship, Vanderbilt University, Department of Pharmacology, Division of Clinical Pharmacology
1977 - 1980	Career Development Award in Clinical Pharmacology - Pharmaceutical Manufacturer's Association Foundation
1981 - 1992	Elected Member, Executive Committee - Clinical Pharmacology Division, American Society for Pharmacology and Experimental Therapeutics
1982	Fellow, American College of Physicians
1985	Fellow, American College of Cardiology
1985	Fellow, Council on Clinical Cardiology, American Heart Association
1990	Recipient of the American Society for Clinical Pharmacology and Therapeutics Rawls-Palmer Award for impact on the practice of medicine
1992	Elected "Teacher of the Year" by Medical Interns and Residents, Georgetown University Department of Medicine

Awards and Distinctions (cont'd.)

1992	Nominee, Golden Apple Award, Georgetown University Medical Students
1994	Chosen by physician colleagues to be included in the 1994-95 editions of *The Best Doctors in America*
1994	Inducted into the Western Kentucky University Hall of Distinguished Alumni
1995	The 1995 Carmela Louise Riker Memorial Lecturer by the Dept. of Pharmacology, Oregon Health Sciences University, Portland Oregon
1995	Chosen by physician colleagues to be included in the 1996-97 editions of The *Best Doctors in America: Southeast Region*
1996	Recipient of the American College of Clinical Pharmacology Distinguished Investigator Award.

Advisory Committees

NIH/VA Research Advisory Committees

1981 - 1984	Member, National Merit Review Board for Cardiovascular Research, Veterans' Administration, Washington, D.C.
1982 - 1986	Member, Pharmacological Sciences Study Section, National Institute of General Medical Science
1987 - 1995	Co-Chair, Executive Committee, Cardiac Arrhythmia Suppression Trial, NHLBI, NIH
1992 - 1996	Member, Clinical Trials Review Committee, National Heart, Lung, and Blood Institute, NIH
1993 - 1997	Member, Data Safety and Monitoring Board of the clinical trial of Antiarrhytbmics vs. Implantable Cardioverter Detibrillators (AVID), National Heart, Lung, and Blood Institute, NIH
12/5-6/94	NCI/FTC Advisory Committee on Test Methods for Determining Tar, Nicotine, and Carbon Monoxide in Cigarettes.

FDA Advisory **Committees**

1982 - 1986	Member, National Cardio-Renal Advisory Committee, Food and Drug Administration
1983 - 1988	Member, Initial Review Committee - Orphan Products Development, Food and Drug Administration
1994	Ad hoc consultant to the Antiviral Drugs Advisory Committee of the FDA on an oral formulation of ganciclovir for CMV retinitis
1994 - 1995	Ad hoc consultant to Antiviral Drugs Advisory Committee of the FDA
1995 - Present	Special consultant to FDA, Center for Drug Evaluation and Research

Advisory Committees--FDA Advisory Committees (cont'd.)

8/18/96-8/17/98 FDA Center for Food Safety & Applied Nutrition Advisory Committee on Ephedra Products

Miscellaneous Research Advisory Committees

1982 - 1984	Member, Test Review Committee National Board of Medical Examiners
1982 - 1984	Member, Grant Review Committee, Tennessee Heart Association
1986 - 1987	Member, Executive Committee of the Scientific Advisory Board, Second International Symposium on Cardiovascular Pharmacotherapy, October, 1987
1988 - 1989	Member, Executive Committee for Scientific Advisory Board, Third International Symposium on Cardiovascular Pharmacotherapy, October, 1989.
1992 - 2000	Member, USP Expert Advisory Panel on Cardiovascular and Renal Drugs

Industrial Research Advisory Committees ,

1982 - 1986	Bristol Myers Cardiovascular Advisory Committee
1993 - 1999	Member, Selection Committee of the Merck Sharp & Dohme International Fellowships in Clinical Pharmacology
1994 - Present	Otsuka Cardiovascular Advisory Committee
1994 - Present	Clinical Pharmacology Advisory Board, Therapeutic Discovery Corp./Alza, Palo Alto, CA
1996 - Present	Technology Advisory Board, Hewlett Packard, Palo Alto, CA

Public Service

5/ 2190	Testified for the American Heart Association before the United States House of Representatives Appropriations Subcommittee on V.A., H.U.D. & Independent Agencies to increase V.A. research funding
5/17/90	Testified for the American Heart Association before the United States Senate Appropriations Subcommittee on V.A., H.U.D. & Independent Agencies to increase V.A. research funding
5/30/91	Represented the American Heart Association at the AHA, American Cancer Society, American Lung Association united as the Coalition on Smoking OR Health, press conference for Smoke Free Skies
2/27/92	Represented the American Heart Association at the AHA, American Cancer Society, American Lung Association united as the Coalition on Smoking OR Health, press conference announcing the filing of anti-tobacco advertising petitions to the FDA & the FTC
1/ 6193	Represented the American Heart Association at the AHA, American Cancer Society, American Lung Association united as the Coalition on Smoking OR Health, press conference on tobacco priorities for the 103rd Congress

Public Service (cont'd.)

4/28/93	Represented the NHLBI Constituency Group before the United States Senate Appropriations Subcommittee on Labor, H.H.S. & Education to increase NHLBI funding
5/17/93	Testified for the American Heart Association before the United States Senate Appropriations Subcommittee on V.A., H.U.D. & Independent Agencies to increase V.A. research funding
5/ 3/94	Testified for the American Heart Association before the United States House of Representatives Appropriations Subcommittee on V.A., H.U.D. & Independent Agencies to increase V.A. research funding
10/13/94	Participated in the Open Public Hearing sponsored by the FDA Cardiovascular and Renal Drugs Advisory Committee and the Symposia on Drug Interactions
12/5-6/94	Member of the Ad Hoc Committee of the President's Cancer Panel to consider the FTC test method for determining tar, nicotine, and carbon monoxide levels in cigarettes
4/3/95	Testified for the American Heart Association at the AHA, American Cancer Society, American Lung Association united as the Coalition on Smoking OR Health before the House Agriculture Appropriations Subcommittee to present testimony addressing FY 96 appropriations
4/6/95	Testified for the American Heart Association before the United States House of Representatives Appropriations Subcommittee on V.A., H.U.D. & Independent Agencies to increase V.A. research funding
1995 - present	Scientific Advisor, The Sudden Arrhythmia Death Syndromes Foundation
2/22/96	Testified before the United States Senate Subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Committee on Appropriations hearings on FDA reform
3/05/96	Testified before the United States House of Representatives Subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Committee on Appropriations hearings on FDA reform
5/10/96	Testified for the American Heart Association before the United States House of Representatives Appropriations Subcommittee on V.A., H.U.D. & Independent Agencies to increase V.A. research funding
3/19/97	Presentation in Capitol Hill briefing on behalf of the Society for the Advancement of Women's Health Research and the Healthcare Leadership Council

Editorial Activities

1980 - 1993	Member of Editorial Board, ***Journal of Cardiovascular Pharmacology***
1982 - 1986	Member of Editorial Board, ***Annals of Infernal Medicine***
1984 - 1990	Member of Editorial Board, *Rational* ***Drug Therapy***
1984 - 1988	Member of Editorial Board, ***American Journal of Cardiology***

Editorial Activities (cont'd.)

1984 - Present	Associate Editor, ***Clinical Pharmacology and Therapeutics***
1985	Guest Editor, Supplement to ***Circulation*** entitled "Role of Programmed Ventricular Stimulation in Evaluation of Investigational Antiarrhythmic Drugs." Circulation 1985;73(2).
1988	Guest Editor, Supplement to the ***American Journal of Cardiology*** entitled "Evaluation of Response to Antiarrhythmic Therapy. " Am J Cardiol 1988;62(12).
1988 - 1991	Member of Editorial Board, ***Circulation***
1990 - Present	Member of Editorial Board, ***Journal American College of Cardiology***
1990 - Present	Clinical Pharmacology Section Head, ***Cardiology***
1991 - Present	Member of Editorial Board, ***Clinical Cardiology***
1993 - Present	Member of Editorial Board, ***PACE***
1993 - Present	Member of Editorial Board, ***Therapeutic Drug Monitoring***
1994 - 1997	Member of Editorial Board, ***Journal of Cardiac Electrophysiology***

Member, Manuscript Review Committees for ***Journal of the American Medical Association, New England Journal of Medicine, Annals of Internal Medicine*** and ***Chest.***

Professional and Learned Societies

1967 - 1985	Member, The Society of ***Sigma XI***
1968 - 1985	Member, Society for Experimental Biology and Medicine
1969 - Present	Member, American Society for Pharmacology and Experimental Therapeutics
1974 - Present	Fellow, American College of Clinical Pharmacology
1976 - Present	Member, American Federation for Clinical Research
1977 - 1988	Member, Nashville Academy of Medicine
1978 - Present	Member, American Society for Clinical Pharmacology and Therapeutics
1979 - 1982	Member, The American College of Physicians
1980 - 1988	Member, Southern Society for Clinical Investigation
1982 - 1986	Member, Joint Advisory Committee on Cardiovascular Drugs to the FDA for the American College of Cardiology and the American Heart Association
1982 - Present	Fellow, The American College of Physicians
1983 - 1984	Member, Board of Regents, American College of Clinical Pharmacology
1985 - Present	Fellow, The American College of Cardiology
1985 - Present	Fellow, Council on Clinical Cardiology of the American Heart Association
1986 - 1990	Member, Fellowship Committee, North American Society for Pacing and Electrophysiology
1986 - 1991	Chair, Joint Advisory Committee on Cardiovascular Drugs of the American College of Cardiology and the American Heart Association

Professional and Learned Societies (cont'd.)

1988 - 1991	Vice-Chairman, Section on Cardiovascular and Pulmonary Pharmacology, American Society for Clinical Pharmacology and Therapeutics
1988 - 1992	Representative of Association for Medical School Pharmacology to the American Association of Medical Colleges, Council of Academic Societies
1988 Present	Member, Association for Medical School Pharmacology
1989 - Present	Member, American Board of Clinical Pharmacology
1991 - 1995	Chairman, Section on Cardiovascular and Pulmonary Pharmacology, American Society for Clinical Pharmacology and Therapeutics
1991 - Present	Member, Public Affairs Policy Committee of the American Heart Association
1992 - Present	Member, Editorial Advisory Council & Publications Committee, American Society for Clinical Pharmacology and Therapeutics
1992 - Present	Secretary-Treasurer, American Board of Clinical Pharmacology
1992 - 1995	Member, Committee on Coordination of Scientific Sections, American Society for Clinical Pharmacology and Therapeutics
1992 - 1994	Secretary-Treasurer, American Board of Clinical Pharmacology
1992 - 1995	Member, Public Affairs Committee, American Society for Pharmacology and Experimental Therapeutics
1993 - 1995	Member, Government Affairs Committee, American Society for Clinical Pharmacology and Therapeutics
1993 - 1996	Member, Executive Advisory Committee, American Society for Clinical Pharmacology and Therapeutics
1994 - 1996	Elected Councilor of Association for Medical School Pharmacology
1994 - 1996	Member, Accreditation of Programs Committee, American Board of Clinical Pharmacology
1994 - 1996	Chair, Nominations Committee, American Board of Clinical Pharmacology
1994 - 1997	Member, Substance Abuse Committee, American Society for Clinical Pharmacology and Therapeutics
1995 - 1998	Member, Committee for the Promotion of Basic Science (CPBS), North American Society of Pacing and Electrophysiology
1995 - Present	Chair, Government Affairs Committee, American Society for Clinical Pharmacology and Therapeutics
1996 - 1997	Member, Long Range Planning Committee, American Society for Clinical Pharmacology and Therapeutics
1996 - 1998	President, Association for Medical School Pharmacology (Chairs Society)

University and Hospital Committees

Vanderbilt University

1979 1984	Chair, Pharmacy and Therapeutics Committee

University and Hospital Committees (cont'd.)

1980 - 1988	Member, Scientific Advisory Committee for the Clinical Research Center
1982 - 1983	Chair, Standing Policy Committee Biomedical Sciences
1982 - 1983	Member, Faculty Advisory Committee
1982 - 1984	Member, Faculty Advisory Board for Biomedical Research Support Grants
1984 - 1988	Member, Pharmacy and Therapeutics Committee
1985 - 1988	Member, Committee on Graduate Medical Education

Georgetown University

1988 - Present	Chairman, Advisory Committee, Clinical Research Center
1988 - Present	Member, Executive Faculty Committee
1988 - Present	Member, Executive Committee, Lombardi Cancer Center
1988 - 1994	Vice-Chair, Pharmacy Committee of tbe University Hospital Executive Staff
1988 - 1990	Faculty Associate, Institute for Health Policy Analysis
1989 - 1994	Chairman, Dean's Advisory Committee for MD/PhD Training Program
1989 - 1994	Co-Chairman, Medical Center Task Force for Cardiovascular Planning
1991 - 1995	Member, Medical Center Executive Council
1992 - 1994	Member, Executive Committee and Internal Review Board for Brain Tumor Research Center
1992 - 1993	Member, Department of Medicine Task Force on Fellowship Education
1992 - 1994	Member, Committee on Appointments and Promotions, Dept. of Medicine
1992 - Present	Member, Committee on Education, Executive Faculty, School of Medicine
1993 - Present	Member, Steering Committee for the Interdisciplinary Pharmacological Sciences Training Program
1994 - 1996	Chair, Pharmacy and Therapeutics Committee
1994 - 1995	Member, Research Resources Facility Task Force
1994 - 1995	Secretary for the Executive Faculty of the School of Medicine
1995 - Present	Member, Search Committee for a chairman of Dept. of Microbiology and Infectious Disease
1996 - Present	Chair, Clinical Research Center Scientific Advisory Committee, Georgetown University Medical Center

Research Activities

University of Louisville

1964 - 1968	Study of the stereospecificity of the renal glucose transport mechanism in animals and the effects of various drugs and heavy metals on this process. (Original articles l-4)

Research Activities (cont'd.)

Meyer 'Laboratories

1968 - 1910 Study of the metabolism of sulfur-containing amino acids in zinc deficient animals. (Original Articles 5-6)

1969 - 1971 Study of the effect of phosphodiesterase inhibitors on atherogenesis in experimental models. (Original Article No. 7)

Vanderbilt University

1975 - 1976 Clinical evaluation (Phase I-II) of tocainide HCl in the treatment of ventricular arrhythmias. (Original Articles No. 8, 11, 15 and 20) Studies of antagonism of the antihypertensive and sympathoplegic effects of guanethidine by ephedrine in animals and man. (Abstract No. 9)

1976 - 1982 Evaluation of the biochemical mechanism of procainamide-induced lupus erythematosus. (Original Articles 9, 10, 12-14, 16, 18, 27, 28, 42, 43, 58)

1980 - 1982 Evaluation of the clinical pharmacology of potential antiarrhythmic and antifibrillatory agents [mexiletene (37), flecainide (30), encainide (21), N-acetylprocainamide (22), meobentine (46), sotalol (54), and bretylium (48)] in patients with arrhythmias.

1982 - 1987 Evaluation of electrophysiological effects of low (beta-blocking) and high plasma levels of propranolol in animals and in patients with arrhythmias. (Original Articles 17, 24, 34, 39, 44) Identification of the antiarrhythmic efficacy of the non-beta blocking isomers, d-propranolol and d-sotalol in animals and patients (supported by HL 26782, Original Articles 73, 93, 95, 106)

The role of pharmacogenetic factors and metabolites in the efficacy of antiarrhythmic agents [quinidide (65), encainide (41), propafenone (74), and lidocaine (78)] was evaluated in animals and man.

1982 - 1987 Principal Investigator for the Vanderbilt site of the NIH-sponsored Cardiac Arrhythmia Pilot Study (CAPS).

1987 - 1988 Principal Investigator for the Vanderbilt site of the NIH-sponsored Cardiac Arrhythmia Suppression Trial (CAST), evaluating the effects of antiarrhythmic therapy on sudden death mortality in patients with recent myocardial infarction.

Research Activities (cont'd.)

Georgetown University

1988 - 1991 **Determination** of the clinical relevance of genetically determined polymorphic metabolism of antiarrhythmic drugs [encainide (51, 81) and propafenone (64, 94)].

Research Activities - Current Research

The actions of antihistamines, their isomers and their metabolites on potassium currents in isolated feline myocytes are being compared using voltage clamp techniques (104, 106). The mechanism of drug-induced sudden death is being examined in animal and tissue models. Clinical and laboratory research is examining the role of sex hormones in control of cardiac repolarization, expression of potassium channels and response to potassium channel blocking drugs.

Previous Federal and Peer-Reviewed Research Support

1) The Electrophysiology of Beta-Receptor Antagonists. Raymond L. Woosley, M.D., Ph.D., Principal Investigator; RO1-HL26782-08, $350,563/yr., 12/1/81-11/30/88.

2) Project Director in PPG: Determinants of Variable Response to Drugs, G. Wilkinson, P.I., 1981-88.

3) Cardiac Arrhythmia Pilot Study. NIH, Clinical Trials Branch. R.L. Woosley, M.D., Ph.D., Principal Investigator, $652,340.00, 1982-1987.

4) Cardiac Arrhythmia Suppression Trial. NIH, Clinical Trials Branch. R.L. Woosley, M.D., Ph.D., Principal Investigator, $1,225,939.34, 1987-1988.

5) Pharmaceutical Manufacturers' Association Foundation Clinical Pharmacology Faculty Development Award. Raymond L. Woosley, M.D., Ph.D., P.I., 1988-1990, $50,000.

6) Showa Denko Research Foundation - Patterns of Xenobiotic Metabolism in the Eosinophilia Myalgia Syndrome', 1991-94, $196,600.

7) American Heart Association - HLA DR & DO Alleles in African-Americans with Idiopathic Dilated Cardiomyopathy, 1993-94, $20,000.

8) NIDA - Electrocardiographic effects of cocaine, 1993-94, $24,000.

9) NIGMS Training Grant in Clinical Pharmacology. Raymond L. Woosley, M.D., Ph.D., P.I., GM083816 1990-1995; $441,450.

Current Research Support (Principal Investigator)

FDA Collaborative Agreement for Clinical Research, Oct. 1991 - June 30, 1997, $2,032,648.

NM - Grant #RO1 HL54590 - Arrhythmogenic Actions of Antihistamines, 08/01/95 - 07/31/00; $960,952.

Pharmaceutical Research Grants for 1995-97:

Pfizer Research
Abbott Laboratories
Novartis Pharma, Inc.

Current Research Support (Co-investigator)

NCI/NIH - Grant #U01 CA 62500-02 (Michael J. Hawkins, MD, P.I.) - Early Clinical Trials of Anti-Angiogenesis Agents, 03/01/94 - 01/31/98; $166,937; 5% Woosley

Dept. of the Army - Grant #UIS DE950303 (Darrell R. Abernethy, MD, PhD, P.I.) - Phase I Evaluation of Desbutylhalofantrine in Healthy Volunteers; 07/01/96 - 06/30/98; 10% Woosley

Patents

Terfenadine Carboxylate (fexofenadine), Patent #5-375-693, December 27, 1994
Itraconazole Isomer, Patent #05474997, December 12, 1995
Norastemizole, UK Patent #2285219, September 11, 1996

Original Articles

1. Woosley RL and Huang KC. Renal excretion of some isomeric hexoses in the dog. Proc Soc Exp Biol Med 124:20-26, 1967.

2. Huang KC and Woosley RL. Renal tubular secretion of L-glucose. Am J Physiol 214(2):342-347, 1967.

3. Woosley RL and Huang KC. Renal excretion of 3-O-methyl-D-glucose. Proc Soc Exp Biol Med 128:375-381, 1968.

4. Woosley RL, Kim YS and Huang KC. Renal tubular transport of 2-deoxy-D-glucose in dogs and rats. J Pharmacol Exp Ther 173(1):13-20, 1970.

5. Anthony WL, Woosley RL and Hsu JM. Urinary excretion of radiosulfur following taurine-^{35}S injection in zinc deficient rats. Proc Soc Exp Biol Med 138(3):989-992, 1971.

6. Hsu JM and Woosley RL. Metabolism of L-Methionine-^{35}S in zinc-deficient rats. J Nutr 102(9):1181-1186, 1972.

7. Woosley RL and Will D. Influence of theobromine magnesium oleate on experimental atheroma. Proc Soc Exp Biol Med 143(4):1098-1105, 1973.

8. McDevitt DG, Nies AS, Wilkinson GR, Smith RF, Woosley RL and Oates JA. Antiarrhythmic effects of a lidocaine congener, tocainide, 2-amino-2',6'-propionoxylidide, in man. Clin Pharmacol Ther 19(4):396-402, 1976.

9. Carr K, Woosley RL and Oates JA. Simultaneous quantification of procainamide and N-acetylprocainamide with high performance liquid chromatography. J Chromatogr 129:363-368, 1976.

10. Drayer DE, Lowenthal DT, Woosley RL, Nies AS, Schwartz A and Reidenberg MM. Cumulation of N-acetylprocainamide, an active metabolite of procainamide, in patients with impaired renal function. Clin Pharmacol Ther 22(1):63-69, 1977.

11. Woosley RL, McDevitt DG, Nies AS, Smith RF, Wilkinson GR and Oates JA. Suppression of ventricular ectopic depolarizations by tocainide. Circulation 56(6):980-984, 1977.

12. Woosley RL, Drayer DE, Reidenberg MM, Nies AS, Carr K and Oates JA. Effect of acetylator phenotype on the rate at which procainamide induces antinuclear antibodies and the lupus syndrome.. N Engl J Med 298(21):1157-1159, 1978.

13. Vansant J, Woosley RL, John JT and Sergent JS. Normal distribution of acetylation phenotypes in systemic lupus erythematosus. Arthritis Rheum 21(2):192-195, 1978.

14. Can K, Oates JA, Nies AS and Woosley RL. Simultaneous analysis of dapsone and monoacetyldapsone employing high performance liquid chromatog.: a rapid method for determination of acetylator phenotype. Br J Clin Pharmacol 6:421-427, 1978.

15. Higgins SB, Woosley RL, Herrin CB, Compton JL and Harris TR. A minicomputer based system for the quantification of ventricular arrhythmias. In Computers in Cardiology, 5th Conference. Ripley KL and Ostrow HG, eds. IEEE Computer Society, Long Beach, pp. 355-358, 1978.

Original Articles (cont'd.)

16. Freeman RW, Woosley RL, Oates JA and Harbison RD. Evidence for the biotransformation of procainamide to a reactive metabolite. Toxicol Appl Pharmacol 50:9-16, 1979.

17. Woosley RL, Kornhauser D, Smith R, Reele S, Higgins SB, Nies AS, Shand DG and Oates JA. Suppression of chronic ventricular arrhythmias with propranolol. Circulation 60(4):819-827, 1979.

18. Taber DF, Jernigan JD, Watson JT, Carr K and Woosley RL. N-desethylacecainide is a metabolite of procainamide in man; convenient method for the preparation of an N-dealkylated drug metabolite. Drug Metab Dispos 7(5):346, 1979.

19. Crook JE, Woosley RL, Leftwich RB and Natelson EA. Agranulocytosis during combined procainamide and phenytoin therapy. South Med J 72(12):1599-1600, 1979.

20. Roden DM, Reele SB, Higgins SB, Carr RK, Smith RF, Oates JA and Woosley RL. Tocainide therapy for refractory ventricular arrhythmias. Am Heart J 100(1):15-22, 1980.

21. Roden DM, Reele SB, Higgins SB, Mayol RF, Gammans RE, Oates JA and Woosley RL. Total suppression of ventricular arrhythmias by encainide: pharmacokinetic and electrocardiographic characteristics. N Engl J Med 302(16):877-882, 1980.

22. Roden DM, Reele SB, Higgins SB, Wilkinson GR, Smith RF, Oates JA and Woosley RL. Antiarrhythmic efficacy, pharmacokinetics and safety of N-acetylprocainamide in human subjects: comparison with procainamide. Am J Cardiol 46:463-68, 1980.

23. Higgins SB, Woyce GM, Roden DM, Harris TR, Oates JA and Woosley RL. An arrhythmia analysis system with patient by patient validation. In '"Introduction to Automated Arrhythmia Detection", Computers in Cardiology, 7th Conference. Ripley KL and Murray A, eds. IEEE Computer Society, Long Beach, pp. 357-360, 1981.

24. Brorson L, Reele S, DuPont W, Woosley R, Shand D and Smith R. Effects of concentration and steric configuration of propranolol on conduction and ventricular repolarization in the dog. J Cardiovasc Pharmacol 3(4):692-703, 1981.

25. Robertson D, Wade D, Workman R, Woosley RL and Oates JA. Tolerance to the humoral and hemodynamic effects of caffeine in man. J Clin Invest 67:1111-1117, 1981.

26. Roden DM, Duff HJ, Reele SB, Woosley RL, Oates JA, Smith RF and Friesinger GC. Recurrent ventricular tachycardia in the absence of overt heart disease: clinical characteristics and response to drug therapy. South Med J 74(9):1090-1094, 1981.

27. Uetrecht JP, Woosley RL, Freeman RW, Sweetman BJ and Oates JA. Metabolism of procainamide in the perfused rat liver. Drug Metab Dispos 9(3):183-187, 1981.

28. Freeman RW, Uetrecht JP, Woosley RL, Oates JA and Harbison RD. Covalent binding of procainamide in *vitro* and in *vivo* ***to*** hepatic protein in mice. Drug Metab Dispos 9(3): 188-192, 1981.

29. Roden DM, Duff HJ, Primm RK, Kronenberg MW and Woosley RL. Control of ventricular pre-excitation and associated arrhythmias by encainide. Am Heat J 102(4):794-797, 1981.

Original Articles (cont'd.)

30. Duff HJ, Roden DM, Maffucci RJ, Vesper BS, Conard GJ, Higgins SB, Oates JA, Smith RF and Woosley RL. Suppression of resistant ventricular arrhythmias by twice daily dosing with flecainide. Am J Cardiol 48(6):1133-1141, 1981.

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Clinical Drug Development May Soon be Accomplished in Less than 3 Years: Will FDA and the Pharmaceutical Industry be Ready?

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Testimony For The Hearing Record

"Reauthorization of the Prescription Drug User Fee Act and FDA Reform"

Subcommittee on Health and Environment
Committee on Commerce
U.S. House of Representatives
Representative Michael Bilirakis, Subcommittee Chairman

ABSTRACT

We envision that **clinical drug development could be accomplished efficiently and safely in less than 3 years in the very near future.** However, "Reforms" are necessary in all sectors involved (pharmaceutical industry, FDA, and academia) in order to achieve this breakthrough.

The **Collaboration on Drug Development Improvement (CDDI)** comprises here-to-fore voluntary initiative among the three sectors that aims to identify approaches for substantially improving the development practices for new therapeutic agents. Consideration should be **given** to funding **the CDDI initiative through the reauthorization of PDUFA or via Congressional aanronriation,**

The Prescription Drug Users Fee Act (PDUFA) has achieved its goals of predictable FDA review times. However. the unintended consequences of curtailed **regulatory research** in **CDER** and constrained **professional** development Of **its** review **scientists impeding adeonate nrenaration for its role in future drug develonment and regulation,**

A solution to the problem of dissemination of information on off-label uses of approved drugs would be the creation of academic Centers **for Research and Education in** Therapeutics **(CERT)** to provide unbiased information and needed research on off-label uses. **CERT should be considered for funding via PDUFA or FDA appropriation**.

Quantity and quality of evidence required to establish proof of effectiveness is inconsistently applied by FDA. **FDA's recent draft clarifications of this exnlain the**

rationale for aast and present policies but fall short of embracing the full breadth of modern scientific concepts and techniques of effectiveness demonstration.

A new process for appeal and resolution of scientific disagreements between FDA and industrial or academic scientists is needed with mechanisms to guarantee no FDA retaliation against those who engage the process.

Reauthorization of PDUFA is an important opportunity to consider funding mechanisms for innovative programs (CDDI, CERT), critical FDA scientific staff activities (regulatory research at CDER and professional development), and key FDA reforms (evidentiary standards of effectiveness and dispute resolution).

INTRODUCTION

Good afternoon Chairman Bilirakis and Members of the Subcommittee. I am honored to be invited to share my views regarding drug development and regulation, particularly on reauthorization of the Prescription Drug User Fee Act and FDA reform.

My name is Carl Peck. I am a physician trained in mathematics and chemistry, and Board Certified in Internal Medicine and Clinical Pharmacology. I direct the Center for Drug Development Science (CDDS) at Georgetown University Medical Center, where I am Professor of Pharmacology and Medicine. CDDS is an independent academic institution that maintains conflict-of-interest free collaborations with industry, government and other academic scientists. Prior to establishing the Georgetown Center in 1994, I served for 26 years in the U.S. Army Medical Research and Development Command and the US. Public Health Service. From 1987 to 1993 I was Director of FDA's Center for Drug Evaluation and Research, during which time I participated in the groundwork for implementation of the first Prescription Drug User Fee Act,

I founded the CDDS to advance the practices of drug development to vastly improve levels of informativeness and efficiency. We are achieving this through research, education' and technical assistance programs. Coordinated by a small staff, our international network of academic, industry and regulatory scientists are identifying key opportunities for improvement of drug development programs. In order to maintain a practical focus, Center faculty, staff, and associates work directly with pharmaceutical

[1] CDDS has recently sponsored a series of international workshops on methodological advances in clinical drug development, including compliance assessments in clinical trials, computer simulation of clinical trials, and accelerated clinical development of active metabolites and stereoisomers. The Center's first full educational course, "Clinical Development of New Drugs and Therapeutic Agents: Art, Science, and New Frontiers" will take place at Stanford University, July 8-l 1, 1997.

developers in planning, analyzing and guiding actual drug development programs,

A CDDS Vision of Drug Development in the Near Future

We envision a very different paradigm for drug development than exists today. This paradigm will be dependent on conditions and incentives that favor innovation in scientific methods and management practices in evaluating new therapeutic agents. Our vision contrasts sharply with contemporary practices that involve tens to hundreds of clinical trials that may be flawed or have failed in design or performance, and excessive numbers of trial subjects, observations, and costs that require many years to accomplish. We propose a highly compressed, critically informative, efficient and economical development approach that entails two developmental scientific investigations and one clinical trial con'rirming effectiveness. These are:

1. **Clinical Pharmacology in Normal Human Subjects or Mildly Ill Patients** -- a comprehensive, exploratory clinical investigation in normal subjects or patients to determine a drug's actions in humans.
2. **Clinical Pharmacology in Ill Patients** -- a scientifically rigorous, proof-of-therapeutic-concept investigation in patients with a targeted disease that documents discovery of optimally safe and effective dosage.
3. **Confirmatory Effectiveness Trial** -- an unequivocal demonstration of effectiveness and safety in a multi-center (and possibly multi-national) clinical trial, with an adequate number of subjects receiving the new therapy under typical conditions of use.

A small number of developmental investigations, such as bioequivalence or drug interaction trials, may also be undertaken in conjunction with the three principle investigations. **Using this approach. clinical drug development time from IND approval to NDA filing dates should be less than 3 years for most new drugs.** Extensions beyond 3 years of clinical development might occur for confirmatory trials of new treatments for slowly progressing chronic diseases.

Much of the knowledge and technology for achieving this new paradigm is already available or is rapidly emerging. Modern clinical pharmacology enables discovery of what a patient's body does to an administered drug (pharmacokinetics) and what a drug does to a patient's body (pharmacodynamics). Clinical trial designs and data analysis techniques for confirmatory effectiveness testing are well known. CDDS is researching emerging technologies for facilitating improved drug development efficiency such as computer simulation of clinical trials[2].

To achieve this goal of an improved drug development process, all groups involved must work collaboratively. We believe that the **CDDI initiative (described below) is an** important pathway to this breakthrough in drug development practices.

Collaboration on Drug Development Improvement (CDDI)

On May **2,** 1996, I presented my views to your subcommittee on whether it is

[2] Although computer simulation in product development is extensively used in many non-pharmaceutical industries (e.g. aerospace, automotive and computer), this technology has not been developed for planning and optimizing clinical trials. Since its inception, CDDS has championed the development, evaluation, and application of simulation of clinical trials as a new tool to increase the quality and success potential of clinical trials. The Center will sponsor a conference on simulation of clinical trials, "Modeling and Simulation and Analysis Workshop: Tools for Efficient Clinical Trials", Washington DC, November IO-11, 1997.

possible to facilitate the development and approval of new drugs and biological products without compromising safety and effectiveness[3]. I focused on the need for bold improvement in drug development practices, particularly in reducing the number of flawed, failed, or unnecessary human clinical trials. Citing the FDA's and the pharmaceutical industry's shared responsibility for improving drug development, I described a pathway for improvement using advances in drug development science, especially clinical pharmacology and statistical data analysis techniques for proving effectiveness. I predicted that streamlining and modernization of effectiveness testing methods could result in reductions in drug development times and more successful employment of human research subjects.

Following the Subcommittee Hearing on June 17-18, 1996, CDDS co-sponsored with FDA (CDER) and FDLI a public conference, "Drug Development: Who Knows Where the Time Goes?". Participants were informed of the strengths and weaknesses of contemporary drug development practices by academic, industry and regulatory scientists. Significantly, attendees to the conference recommended that a formal collaboration among the three sectors be initiated with the goal of identifying approaches for substantially improving the development practices for new therapeutic agents

Promptly following the conference, the Collaboration on Drug Development Improvement (CDDI) was founded (Appendix 1). Driven by key scientists at CDER (especially Drs. Janet Woodcock and Roger Williams) and CDDS, the representation on the CDDI Steering Committee was broadened to include representatives from CBER,

[3] "Streamlining and Modernizing Drug Development", Testimony by C. Peck for the Hearing Record, Subcommittee on Health and Environment, U.S. House of Representatives, May 2, 1996

PhRMA, and BIO. The Steering Committee met on September 25 and December 5, 1996, to establish the purpose, scope, goals, and future actions. An issues identification meeting is planned for the near future to begin the real work of the CDDI. **However, the lack of funding for this voluntary initiative is jeopardizing its ability to continue its programs. We recommend that your subcommittee consider PDUFA or Congressional appropriation as funding mechanisms for the CDDI initiative.**

PDUFA: Accomaiishments and Unintended Consequences

The Prescription Drug User Fee Act (PDUFA) is a great success, Since its implementation in 1993, to the credit of the leadership and scientific review staff of FDA and the new drug sponsors submitting high quality New Drug and Product License Applications (NDAs and PLAs), review times of priority and standard NDAs and PLAs have been reduced to 6 to 12 months, Moreover, the substantial review backlog has been eliminated. FDA is now properly attending to the processes and procedures necessary to meet review time standards, Congress, PhRMA, BIO, and FDA all deserve acknowledgment for their contributions to this landmark achievement.

However, there have been two unintended consequences of the restricted uses of PDUFA derived funds and application review time commitments (coupled with limited non-PDUFA operational resources): critical regulatory research[4] in CDER, such as

[4] CDDS recognizes that focused, applied regulatory research at FDA is necessary for advancing the scientific basis for regulatory standards (e.g. manufacturing quality assessments, bioequivalence study procedures based on pharmacodynamic endpoints, pharmacometric and simulation based investigations of regulatory value, validation procedures for surrogate endpoints, etc.) and adverse reaction database derivation and analyses. A zero-based assessment of all FDA research should be undertaken and basic research that is not immediately relevant to regulatory standard setting or enforcement should be redirected or transferred to an appropriate government institution (e.g. NIH).

surveillance of adverse reactions, has been curtailed, and professional development of its scientific staff has been constrained. **Because FDA's capacity to implement significant reforms to prepare for its advisory and regulatory roles in future drug development is critically impaired by these deficiencies, reauthorization of PDUFA should not be undertaken without their resolution,**

Some FDA Reform Issues:

Dissemination of off-label uses of approved drugs and Centers for Research and Education in Research (CERT). Physicians must have access to current, scientifically reliable and balanced information about drugs in order to make informed decisions for their patient's treatment. Pharmaceutical and device companies should be permitted to disseminate copies of peer-reviewed scientific articles that report scientifically sound clinical trials that have evaluated off-label indications for their products. The companies should be required to disclose their financial interests and that the indication is not FDA-approved, i.e. "off-label." However, dissemination of this information should be monitored by an independent body prepared to respond to prescribing physicians, health care professionals and the public with balanced, unbiased information about the off-label uses of drugs.

The Nation's academic medical centers have the medical, pharmacological, and educational expertise to teach practicing physicians, nurses, pharmacists and the public about drugs that are prescribed, administered, dispensed or purchased. A consortium of federally-authorized regional academically-based centers **(CERT)** has been proposed as a

means to address this problem (Appendix 2). The consortium would be selected through a peer-review mechanism and would be affiliated with FDA so that activities will be coordinated at a national level. Each Center would include pharmacologists, clinical pharmacists and clinical pharmacists, all conducting needed research and educational programs about the optimal use of medications. CERTs should include participation of scientists in the pharmaceutical industry; however, to ensure their objectivity, each CERT should be given independent funding. This independence that allows them to be credible advocates for optimal prescribing. These Centers also should conduct research that industry is unlikely to perform, such as the study of unprofitable off-label indications, and the use of medications in children, the elderly and other understudied populations. **We recommend that your subcommittee consider PDUFA or directed appropriations to FDA as funding mechanisms for the CERT initiative.**

Standards of Evidence of Effectiveness. As a result of the 1996 Senate and House Hearings on FDA reform the FDA Draft Guidance, "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" was published on March 13, 1997. Prompted by CDDS testimony on the redundant requirement in modem development programs for more than one confirmatory clinical trial to prove effectiveness, FDA scientists have prepared a comprehensive statement of the Agency's current policies and views on the legal and scientific aspects of quantity and quality of evidence necessary to support effectiveness of new therapeutic agents. FDA deserves credit for its review and explication of its policies on this issue. **Nevertheless, FDA's**

draft guidance falls short of embracing the full breadth of cutting edge, scientific **concepts** and **techniques** of effectiveness demonstration. CDDS is preparing a detailed critique of the draft guidance to be submitted to the Agency as a public comment,

Scientific Dispute Resolution and Appeals. Aside from many useful guidances and policy statements the Agency promulgates, there are and always will be disagreements over what constitutes sufficient quality and quantity of data to support FDA's conclusions about the safety and effectiveness of new therapies, as well as the investigations necessary to generate such data. Many new drugs for medical conditions with no available effective treatments are novel. The standards of evidence for these new therapeutic agents are sometimes arbitrarily established by the FDA reviewing division with insufficient input from external scientific experts. Currently, the only mechanism to resolve scientific disagreements about test methods, and what outcome measures and/or quantity of data are sufficient, is to bring the issues to the Division, Office or Center Directors. While FDA's standing advisory boards can be called upon to resolve such disputes, in practice many real or perceived disincentives and barriers mitigate this option. Drug developers fear retaliation and retribution when the FDA is not supported in the appeals resolution and often decline to enter into the existing appeals procedure.

To facilitate more efficient resolution of standards of evidence disputes, language could be included in PDUFA II that establishes a mechanism that involves external expert scientists in the IND phase of drug development to recommend to the FDA and the developer what quality or quantity of evidence should be generated

to establish specific safety and/or effectiveness claims. At the request of the sponsoring company, the company and the agency jointly could create the expert panel to resolve disagreements. **An administrative tracking mechanism should be established to ensure that companies that engage the dispute resolution procedure are not penalized in future interactions with FDA.**

"Reform" of All Sectors Involved in Drug Development is Necessary

During the May 2, 1996, Subcommittee Hearing, I presented preliminary results of a pilot study of the contents and qualities of NDAs approved by FDA during 1994-1995, from which we concluded that vast improvements on contemporary drug development are warranted. At that time, our examination of data from 9 of the 52 approved NDAs indicated that contemporary drug development programs appeared to comprise large numbers of clinical trials (44-600+), many of which were not adjudged by FDA to be necessary or of high quality (9%-65%). We have recently expanded this pilot study to 24 NDAs. While our conclusions regarding improvability of drug development remain unchanged, the wide variability in content and quality of these successful programs may provide insights into pathways for improvement. For example, several NDAs were approved with fewer than 10 clinical trials, and FDA adjudged some of these programs to have few, if any, flawed or failed trials.

Thus. we remain convinced that all sectors involved in drug development can and should be "reformed." To be sure, many pharmaceutical firms have been reengineering their approaches to drug development toward fewer, more successful

clinical trials. Nevertheless, inefficient and suboptimal practices persist in contemporary drug development, due in part to lack **of** carefully evaluated new approaches as well as to lack of receptivity of some (not all) FDA staff to newer and novel scientific methods. Although academia is increasingly involved in performance of clinical trials of new therapeutic agents, it has received few incentives to respond to the need to invent and investigate novel methodological approaches to scientific drug development.

Reauthorization of PDUFA is an important opportunity to consider funding mechanisms for innovative programs (CDDI, CERT), critical FDA scientific staff activities (regulator?, research at CDER and professional development), and key FDA reforms (evidentiary standards of effectiveness and dispute resolution).

APPENDIX 1

PROPOSAL

COLLABORATION ON DRUG DEVELOPMENT IMPROVEMENT (CDDI)

CBER, FDA
CDER, FDA
CDDS, Georgetown University
BIO
PHRMA

January 21, 1997

Draft Version 1 .O

I. INTRODUCTION

This proposal describes an effort, the Collaboration on Drug Development Improvement (CDDI), that is designed to advance the development process for pharmaceuticals and biopharmaceuticals (medical products). The information developed by the Collaboration will be used to support guidance documents for pharmaceutical scientists on efficient, scientifically sound approaches for development of an investigational medical product. Participating organizations in CDDI are: 1) the Center for Biologics Evaluation and Research (CBER)/FDA; 2) the Center for Drug Evaluation and Research (CDER)/FDA; 3) Georgetown University Medical Center/Center for Drug Development Science (GUMC/CDDS); 4) the Pharmaceutical Research and Manufacturers of America (PhRMA); and 5) the Biotechnology Industry Association (BIO).

II. RATIONALE

Modern drug development requires information to support the translation of candidate therapeutic agents into therapeutically useful products. This information is used to document the utility of new medical products and to satisfy societal interests in allowing safe, effective, and well-labeled medical products into the marketplace. Development of the necessary information to document safety, efficacy, and utility, and to support product labeling involves a highly complex set of scientific and administrative activities. These activities are affected by the needs and interests of the patient and the health care professional, by scientific opportunities, by public health objectives, by commercial factors, and by resource constraints. The scientific framework in which development of a medical product proceeds is dynamic in that new approaches may be developed and older ones discarded. The science-based regulatory framework for development of medical products is also dynamic in that public health objectives may change in response to patient needs and societal interests. Given the dynamic character of these factors and also that the process involves many constituencies-pharmaceutical sponsors, the scientific and health care communities, the government, and society at large--a potential synergism exists in which involved constituencies could work collaboratively to improve methods and procedures for development of new medical products.

III. BACKGROUND INFORMATION

Current approaches to the development of useful information about investigational medical products may require excessive tie and effort, leading to delay in the availability of needed treatments. In addition, improvements in the way this information is developed could lead to optimal product labeling and use. To address these issues, the Georgetown University Center for Drug Development Science (CDDS), CDER, and the Food and Drug Law Institute sponsored a meeting in June 1996 entitled *Drug Development: Who Knows Where the Time Goes.* The principal goal of the conference was to explore the process that generates information about new medical products and to consider what barriers and constraints exist *in* the process. Following a series of presentations from industry, agency and academia representatives, a panel of experts summarized the presentations and proposed a further collaborative effort to improve methods and procedures for development of new medical products. Following the June 1996 meeting, further discussions occurred to consider the proposals arising from the Georgetown Conference. On September 25, 1996, representatives of Georgetown University Medical Center/CDDS, CDER, CBER, PHRMA, and BIO met and

agreed to consider formation of a collaborative effort, the Collaboration on Drug Development Improvement (CDDI).

IV. PRIOR FDA EXPERIENCE WITH COLLABORATIVE APPROACHES

FDA has worked collaboratively with extramural constituencies on several occasions. Examples include: 1) the National Center for Food Safety and Technology (Attachment A); 2) the Joint Institute for Food Safety and Applied Nutrition (Attachment B); and, 3) the collaborative product quality research at the University of Maryland at Baltimore (UMAB), which included scientists from FDA, the pharmaceutical industry, and academia (Attachments C and D).

V. PROPOSAL

The mission, scope, goals and objectives, structure, and process of CDDI are discussed in the following paragraphs.

A. Purpose

The purpose of CDDI is to improve substantially the development of pharmaceuticals, including biopharmaceuticals.

B. Scope

The scope of CDDI comprises the preclinical and clinical testing phases in the development of pharmaceuticals, including the post-approval phase. Drug development science and science management methodologies will both be considered.

C. Goals

CDDI will study and advance current and new approaches to substantially improve the efficiency of the drug development and assessment processes by: 1) reducing unnecessary studies and activities; 2) increasing useful information; and 3) improving resource utilization and shortening development times.

D. Structure and Function

Steering Committee

CDDI will be directed by a Steering Committee. Members of the Steering Committee will consist of the Directors of CBER and CDER, one or more representatives from academia, and representatives from PHRMA and BIO. Steering Committee membership should be composed of individuals with science/technical backgrounds and who also have experience in management.

Technical Committees

Six technical committees will be formed to cover the following areas: 1) Nonclinical Studies; 2) Mechanistic Studies; 3) Empirical Studies; 4) Post Marketing Studies; 5) Science Management; and 6) Novel Approaches. The six technical committees will propose, for Steering Committee approval, programs and projects to develop information to support recommendations to pharmaceutical scientists which may be published as guidance (regulatory and non-regulatory) documents. 'Information' in this context is used broadly to include retrospective and prospective investigations, cumulative understanding of current approaches, literature searches, and associated efforts. Technical Committee members shall possess strong science/technical skills and have experience in the management of science projects.

Working Groups

These groups will supervise the execution of specific projects within a program, work with research site(s) to summarize and report results, and create draft recommendations for further consideration by the supervisory Technical Committee and Steering Committing. Individuals selected for specific working groups should also have strong science/technical skills in specified program/project areas.

E. Process

The Steering Committee will provide general direction to CDDI and oversight to the Technical Committees, including approval of Technical Committee proposals. The Steering Committee will also review outcomes from programs and projects submitted by a Technical Committee, assess the overall impact of CDDI activities, and determine the need for continuing activities and/or modification in the way the initiative operates.

Technical Committees will define programs and projects within programs, create working groups to focus on these programs and projects, and establish timeframes for completion of work. The Technical Committees will review reports and other information generated from working groups, consider how this information can be used in the drug development and regulatory processes, and make recommendations to the Steering Committee.

Working for specific projects within programs will formulate the intended improvement in drug development as the primary goal of a project. Projects may be executed using academic facilities and staff, industry facilities and staff, and/or agency facilities and staff. Selection of a specific site or sites for conduct of a research project will be the responsibility of the Working Group, with endorsement by the supervising Technical Advisory Committee. Consideration of certain projects may occur competitively via a request for proposal process. A peer review process, executed by the Working Group, with final endorsement by the Technical Advisory Committee, will be established to evaluate competing proposals. After completion of a project, the Working Group will work with the project research site to disseminate the results. Dissemination may occur via publications, workshops, and presentations at meetings of professional societies, Results will also be presented to regulatory agency staff associated with or otherwise interested in the research.

A Working Group will collaborate with the project research site to draft guidance documents for review and endorsement by the Technical Advisory Committee. These will be forwarded to the Steering Committee for concurrence and then to appropriate CBER and CDER policy units for further consideration and, if appropriate, translation into regulatory guidances. Policy units within CDER include the Medical Policy Coordinating Committee and the Pharmacology/Toxicology Coordinating Committee.

Regulatory documents developed by these coordinating committees are submitted to the Director, Regulatory Policy Staff, CDER, and to CDER management for concurrence, finalization, and dissemination. [Need equivalence statements for CBER.] Further review by agency management and counsel is performed as necessary. Regulatory guidance documents developed as a result of an initiative effort will be published in the ***Federal Register.*** Efforts by a technical committee and a working group may also lead to non-regulatory policy and publications that may be useful to pharmaceutical sponsors.

Training Programs When appropriate, a Working Group and the project research site may be requested to develop training modules to aid in the implementation of new regulatory policy recommendations. Training may occur for agency and non-agency staff and other interested individuals. The Working Group, the Technical Committee, and the Steering Committee will work to monitor the impact of regulatory and other policy arising as a result of research programs, address certain questions that may arise as a policy based on a research project/program is implemented, and assist in updating policy as appropriate.

VII. ADMINISTRATIVE ISSUES

A. Governance

One or more memoranda of agreement or cooperative agreements may be developed by CDDI to facilitate the generation of information by the collaboration.

B. Resources

Resources to support CDDI activities could occur in the form of contributions of 1) personnel time, 2) space, and 3) equipment. Financial contributions may derive from public funds (appropriated dollars), public funds associated with PDUFA, and contributions from specific members and groups. For the latter, two general approaches may be considered. One approach is based on funding programs/projects by collaboration members who have an identified interest in a specific research program/project and regulatory outcome. A second approach involves regular contributions by interested participants which are not linked to a specific research program. The second approach allows general functioning of the collaboration Over a specified period of time.

C. Access and Transparency

CDDI deliberations, efforts, and outcomes are expected to be publicly available. The collaboration will develop mechanisms to achieve this objective.

D. Confidential Commercial and Trade Secret Information

CDDI is not intended to disseminate or impact in any way on confidential commercial or trade secret information developed by a pharmaceutical sponsor.

E. Legal Considerations

Cooperative agreements, conflict of interest, intellectual property rights, liability, and other issues, may require consideration by CDDI.

F. National and International Connections

CDDI may work to develop connections with national and international professional societies, academic institutions, and regulatory agencies.

G. Communications and Record-Keeping

CDDI will develop mechanisms to facilitate communications between participants and to maintain records of its activities.

Appendix 2

Centers for Education and Research in Therapeutics - CERT

The United States of America is a medication-oriented society. Each year over 2 billion prescriptions are written, amounting to over eight prescriptions per person, Over two thirds of patient visits to physicians result in at least one new prescription; and often more than one. Over $60 billion is spent each year on prescription drugs and much more on non-prescription drugs. All will agree that medications have contributed positively to our Nation's overall public health and the pharmaceutical industry is to be commended for developing the drugs that have led to major advances in medical care. However, are we utilizing these therapies optimally? Are physicians, nurses, pharmacists and the public being taught how best to use these drugs? Prescribing errors are the second largest cause for a malpractice claim in the US today. Of these errors, 42.4 percent result in death or permanent disability. Fifteen percent of hospitalized patients suffer a significant adverse reaction to a medication and five percent of medical admissions to hospitals are due to adverse drug reactions. Recent estimates indicate that at least 25 percent of prescriptions for the elderly are inappropriate and dangerous., Polypharmacy results in serious and potentially lethal drug interactions with more and more new drugs, such as the newer antihistamines. There is an unmet need to provide physicians more complete information about the drugs they prescribe. The pharmaceutical industry mainly promotes a drug's advantages in approved indications. At the same time the manufacturer is prohibited from promoting unapproved uses of drugs, even if efficacy is generally accepted.

Another important deficiency in our therapeutic knowledge base stems from limitations in the basic and clinical research on the actions of drugs. After demonstrating efficacy and relative safety, the pharmaceutical industry, of necessity, invests its resources into finding the positive attributes of its drugs. Yet, there is additional important research that is not being conducted, e.g. studies of the biochemical or pharmacogenetic mechanisms for drug interactions or adverse drug reactions, actions of drugs in special populations (pediatrics, the very elderly, women, minorities) and efficacy for less than profitable indications. The Nation's academic medical centers have the pharmacologic expertise to conduct this research and they have the trained educators qualified to teach practicing physicians, nurses, pharmacists and the public about the drugs that they prescribe, administer or purchase.

A program of federally-authorized regional academically-based Centers for Education and Research in Therapeutics (CERT) has been proposed as a solution to this problem'. The Centers should be selected by an NIH peer-review mechanism and affiliated with the FDA for coordination of their basic and clinical research. The Centers would include pharmacologists, clinical pharmacologists and clinical pharmacists, all conducting needed research and working with the US Pharmacopeial Convention to educate physicians, nurses, pharmacists and the public about the optimal use of medications. The CERT program should allow participation of scientists in the pharmaceutical industry. However, to assure their objectivity, each CERT should be given independent funding. Legislators are encouraged to enact legislation authorizing the CERT program and to appropriate funds so that these Centers can carry out the mission of conducting independent education and research in therapeutics for our Nation.

1. Woosley, R.L., CERT, Clin. Pharm. Ther. 55:249-255, 1994.

I disclose that neither the Georgetown University Center for Drug Development Science nor I have received federal funds or federal grants during the past fiscal year or during the two previous fiscal years.

Carl C. Peck, M.D.

April 23, 1997

Date

Dr. Raymond L. Woosley

Agency	Contract #	Title, Funding Dates and Funding Amount
NIH	HL54590	Arrhythmogenic Actions of Antihistamines. 8/1/95-7/31/00: $947,949 Direct Costs
FDA	223-93-3011	Evaluate the Status of Selected Drugs for Conducting In-Vivo Studies and Provide the FDA Access to a Clinical Research Facility. 9/3/93-6/30/97: $2,396,881 Direct and Indirect Costs

I disclose that this is current federal funding.

Raymond L. Woosley, M.D., Ph.D.

4/23/97
Date